UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,066	09/24/2004	Ulrich Abel	12874-00001-US	1371

23416 7590 08/11/2010

CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
DESAI, RITA J	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
08/11/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,066	ABEL ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims pending are 1-7, 9, 15 and 16.

Response to the arguments:-

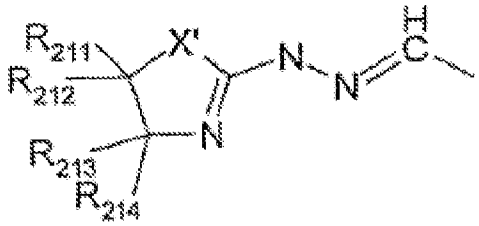
Applicants had submitted a supplemental amendment that had crossed in the mail. In the amendment submitted on 3/11/10 the definition and the variable were changed to R", Y' and several R2, R3, R5, R1 has been changed. The formula Ia and Ib remain the same. The rejection under 35 USC new matter has been withdrawn.

The rejection under 35 USC 112 scope of enablement still stands. The schemes in the specification allows for just a small % of substitutions.

The R2 along with the various R4, R6, R7 has so many generic variables.

R2 means aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, C_2-C_8 alkenylheteroaryl, cycloalkyl, C_1-C_8 alkylcycloalkyl, heterocycloalkyl, C_1-C_8 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y'_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y' = independently selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, and SH, SR21), $(CH_2)_nCH_2NHCOR21$, $(CH_2)_nCH_2OCOR21$, $(CH_2)_nCH_2NHCSR21$, $(CH_2)_nCH_2S(O)mR21$, with n = 0, 1, 2, $(CH_2)_nCH_2SCOR21$, $(CH_2)_nCH_2OSO_2$-R21, $(CH_2)_nCHO$, $(CH_2)_nCH{=}NOH$, $(CH_2)_nCH(OH)R21$, -$(CH_2)_nCH{=}NOR21$, $(CH_2)_nCH{=}NOCOR21$, $(CH_2)_nCH{=}NOCH_2CONR21R22$, $(CH_2)_nCH{=}NOCH(CH_3)CONR21R22$,

$(CH_2)_rCH=NOC(CH_3)_2CONR21R22$, $(CH_2)_rCH=N-NHCO-R23$, $(CH_2)_rCH=N-NHC(O)NH-R23$, $(CH_2)_rCH=N-NHC(S)NH-R23$, $(CH_2)_rCH=N-NHC(NH)NH-R23$, $(CH_2)_rCH=N-NHC(NH)-R23$, $(CH_2)_rCH=N-NHCO-CH_2NHCOR21$, $(CH_2)_rCH=N-O-CH_2NHCOR21$, $(CH_2)_rCH=N-NHCS-R23$, $(CH_2)_rCH=CR24R25$ (trans or cis), $(CH_2)_rCOOH$, $(CH_2)_rCOOR21$, $(CH_2)_rCONR21R22$, $-(CH_2)_rCH=NR21$, $(CH_2)_rCH=N-NR21R22$,



, and the $(CH_2)_r$-chain elongated group $(CH_2)_rCH=N-N-(C_5NX'R211R212R213R214)$ (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_6 alkyl), $-(CH_2)_rCH=N-NHSO_2$ aryl, or $-(CH_2)_rCH=N-NHSO_2$ heteroaryl, with r = 0, 1, 2, 3, 4, 5,

or

R3 means F, Cl, Br, I, OH, OR31, NO_2, NH_2, NHR31, NR31R32, NHCHO, NHCOR31, $NHCOCF_3$, $CH_{3-m}hal_m$ (with hal = Cl, F, and m = 1, 2, 3), or OCOR31, and

R2 means H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_8 alkylaryl, heteroaryl, C_1-C_8 alkylheteroaryl, C_2-C_8 alkenylheteroaryl, cycloalkyl, C_1-C_8 alkylcycloalkyl, heterocycloalkyl, C_1-C_8 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y'_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y' = independently selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, and SH, SR21), $(CH_2)_rCH_2NHCOR21$, $(CH_2)_rCH_2OCOR21$, $(CH_2)_rCH_2NHCSR21$, $(CH_2)_rCH_2S(O)nR21$, with n = 0, 1, 2, $(CH_2)_rCH_2SCOR21$, $(CH_2)_rCH_2OSO_2-R21$, $(CH_2)_rCHO$, $(CH_2)_rCH=NOH$, $(CH_2)_rCH(OH)R21$, $-(CH_2)_rCH=NOR21$, $(CH_2)_rCH=NOCOR21$, $(CH_2)_rCH=NOCH_2CONR21R22$, $(CH_2)_rCH=NOCH(CH_3)CONR21R22$, $(CH_2)_rCH=NOC(CH_3)_2CONR21R22$, $(CH_2)_rCH=N-NHCO-R23$, $(CH_2)_rCH=N-NHC(O)NH-R23$, $(CH_2)_rCH=N-NHC(S)NH-R23$, $(CH_2)_rCH=N-NHC(NH)NH-R23$, $(CH_2)_rCH=N-NHC(NH)-R23$, $(CH_2)_rCH=N-NHCO-CH_2NHCOR21$, $(CH_2)_rCH=N-O-CH_2NHCOR21$,

- The claim reads R8 can independently defined by R5 and R5 can be H and yet it states it can combine to form a ring!.
- The schemes describes only a process of making a limited set of compounds with a specific R2 group and R6, R4 and R7 to be H. Applicants R21 has a long list of variables such as pasted below

  here.

> R21, R22 are independently H, C_1-C_{18} alkyl, C_1-C_{18} alkanoyl, C_1-C_6 alkylhydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 alkylamino-C_1-C_6 alkyl, C_1-C_6 alkylamino-di-C_1-C_6-alkyl, cycloalkyl, C_3-C_6 alkylcycloalkyl, heterocycloalkyl, C_3-C_4 alkylheterocycloalkyl, aryl, aryloyl, C_1-C_4 alkylaryl, heteroaryl, heteroaryloyl, C_1-C_4 alkylheteroaryl, cycloalkanoyl, C_3-C_6 alkanoylcycloalkyl, heterocycloalkanoyl, C_1-C_4 alkanoylheterocycloalkyl, C_1-C_4 alkanoylaryl, C_1-C_6 alkanoylheteroaryl, or R21 and R22, together with the N, form a ring with 4, 5, 6, 7, or 8 members, which may optionally contain still another heteroatom selected from the group N, O, and S,

The starting materials are also not shown. It appears that the large scope is a theoretical scope of the analogs of Fredericamycin.

See Dorwald preface 2005 , which states how difficult it is to synthesis organic compounds.

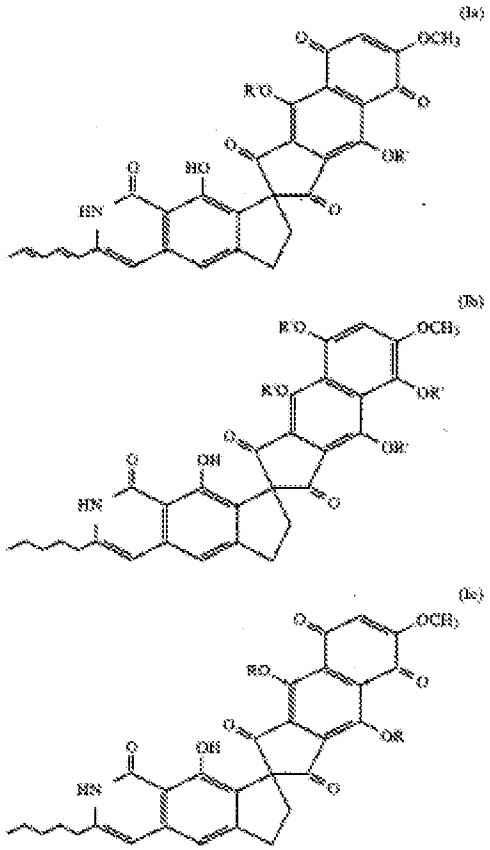
Only the compounds within the scope of the scheme and the table are enabled for making.

State of the prior art :-

US 5166208 which is drawn to Fredericamycin also teaches only the compounds with R4, R6 and R7 as H.

All the prior art compounds have R4, R6 and R7 as an OH group. Yet applicants are claiming a plethora of groups at that position which is included in the definition of R21

Also see US 4, 584,377 which teaches only an acyl at the R 4, R6 and R7 position.



wherein R has the same meaning as defined above, and R' denotes an acyl group.

The Fredericamycin A derivatives (I) of this invention may be prepared by either one of the following processes:

The prior art does not teach the large scope with the various substitutents R21 at R4, R6 and R7 position , as claimed by the applicants, and neither has the applicants shown how to make and use them.

- Claim 9 recites the term "Drug " containing the compounds.

The term Drug is not clearly defined in the specifications.

The pharmaceutical adjutant are, but not the "Drugs".

Is this a method of treating as a drug, the compounds scope is not enabled for treating also.

- R24 and R25 each individually is H, CN and also R21 with is another plethora of substitutents, R24 and R25 together is a cycloalkyl .
- R2 is given by

, and the $(CH_2)_n$-chain elongated group $(CH_2)_nCH$=N-N-$(C_3NX'R211R212R213R214)$ (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_6 alkyl), -

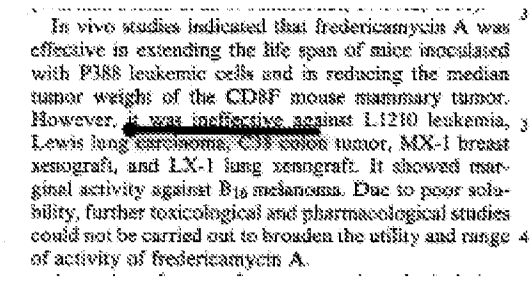
Where are these 4 R groups attached to? The N? or C3 ?

Further applicants argue that the because Fredericamycin treats tumors and that their compounds have a similar structure then theirs also should treat the tumors.

For the sake of arguments, first of all, Fredericamycin has an effect on breast, and leukemia with a marginal effect on melanoma. See Dana Warnick-Pickle.

Second the data shown by the applicants is an average of results obtained for several cell lines, not an average of several test of each cell line. It is confusing because, to see if a drug works on the breast cancer cell, one would not test it on some other cell line. How can one rely on a test result which is an average of many different cell lines?

Applicants have not made the compounds and shown that it is reduced to practice, especially since the US '678 teaches that it does not treat all tumors.



In vivo studies indicated that fredericamycin A was effective in extending the life span of mice inoculated with P388 leukemic cells and in reducing the median tumor weight of the CD8F mouse mammary tumor. However, it was ineffective against L1210 leukemia, Lewis lung carcinoma, C38 colon tumor, MX-1 breast xenograft, and LX-1 lung xenograft. It showed marginal activity against B_{16} melanoma. Due to poor solubility, further toxicological and pharmacological studies could not be carried out to broaden the utility and range of activity of fredericamycin A.

Applicants could overcome this part of the rejection with a timely filed declaration showing the test data for each cell line.

Applicants should also consider the R21 groups for R4, R6 and R7 positions as these have not been reduces to practice and having all these bulky groups as these various positions individually or all at the same time be impossible to make, let alone the fact that it would no longer be a Fredricamycin analog and would no longer be expected to have the same properties and thus would require more data to show that it had the same activity.

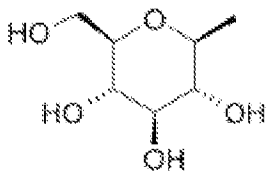
Also in view of the unclear definition of drug and some of the variable it cannot be seen how these compounds are enabled.

The rejection under 35 USC 112 scope still stands.

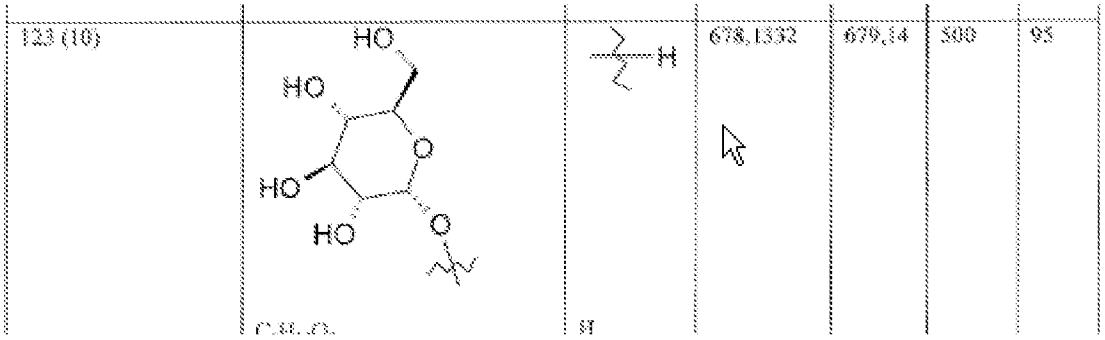
The rejection of the claims under 35 USC 103 over U.S. patents 4,584,377 (Yokoi et al.); 4,673,678 (Misra) and 5,166,208 (Kelly et al.). Duan et al., Delgado et al. and Okimoto et al also still stand.

Applicants argue the examiner says the different groups would encompass sugars and that if the rejection is not withdrawn then to point out where it would encompass a sugar.

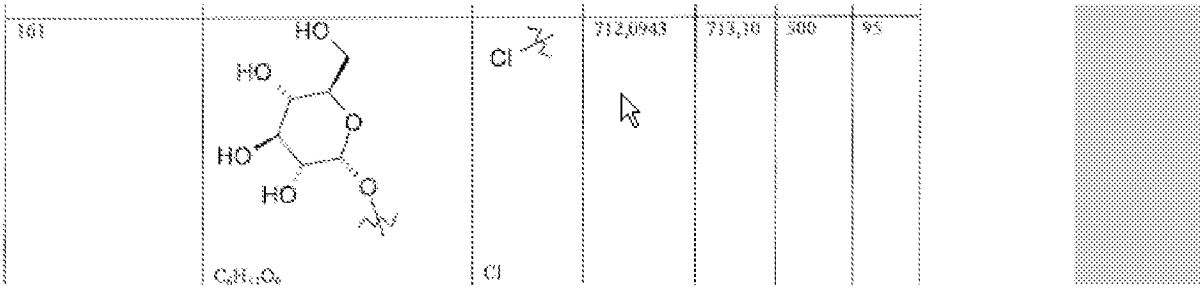
For example, in the diagram 4 page 18 and 19 of the specification see 10/123 R' group. See amendment table 2, page 3,

10/123		678.1	504.0

See page 10 table 3,

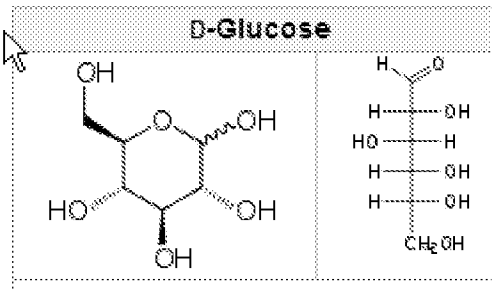


Page 18,



Also eg 199.

See the definition of glucose (sugar) as given by Wikipedia definition , attached. Glucose in solution is given in the form of a ring.

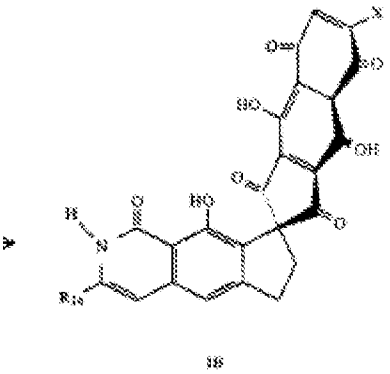


There are several places where applicants have defined the claims are forming a ring with specific hetero groups, however the various combinations such as for the definition of R2 $(CH_2)_nCH{=}CR24R25$ (trans or cis), , R24 and R25 can be R21 and both together can form a ring e.g. alkoxy.

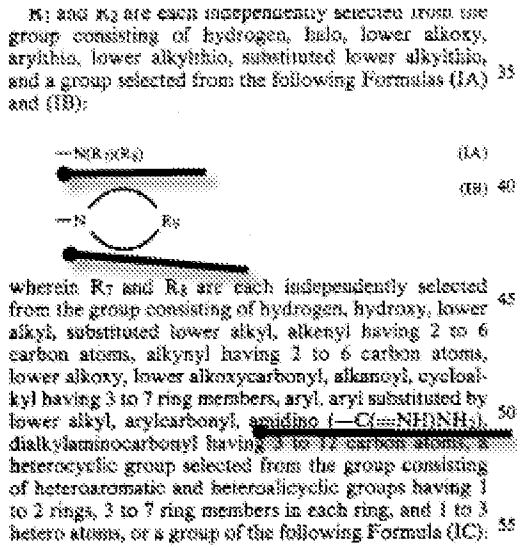
Applicants claims include alkyl substituted by hydroxyl and could include the glucose.

In view of the disclosure in the specification one would expect the compounds could have the glucose. Besides the term "Drugs' is not defined. The specification clearly states that the Fredricamycin with the dextrin is more soluble. See page 21.

The US 5166,208 discloses the compounds of the formula Ib

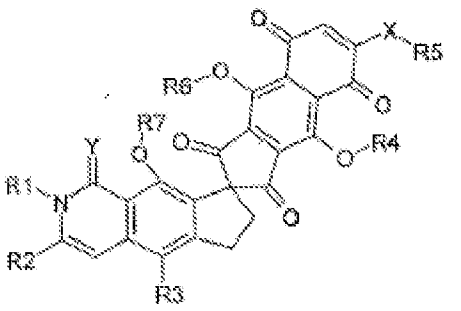


wherein X is a H or a lower alkoxy and R14 and r15 is a lower alkyl, alkenyl and alkonyl. R1 and r2 is independently a H or a NR7 R8, R7 and R8 can form a ring. include several groups such as



These groups are further substituted.

Applicants claims are drawn to, according to the latest version presented as being



wherein X is an O and R5 can be a H.

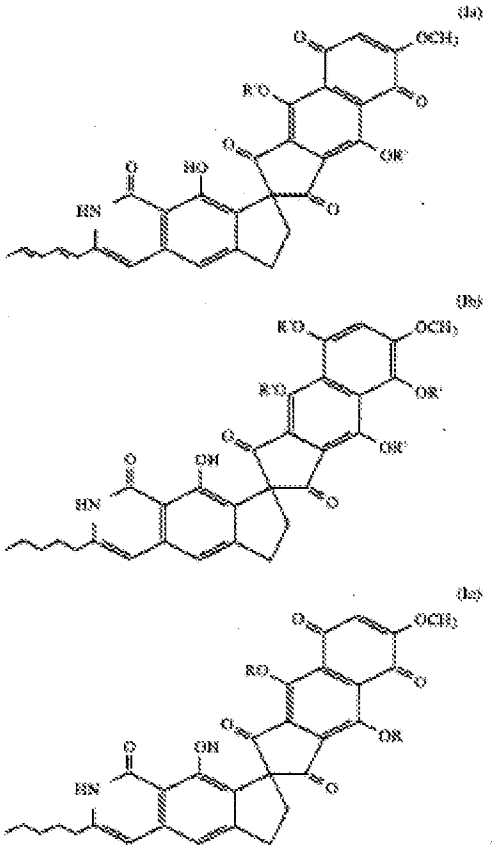
R7 is a H,

R3 is a halogen or an hydroxyl or an N containing group as given on page 14 of the amendment.

R2 can then be an alkyl, alkenyl,

When R3 is a H as is in the prior art then applicants R2 is a other groups which are similar to the R1 or R2 groups of the prior art.

US 4584377 Yokoi also teaches similar compounds of the formula with acyl groups at its R'



wherein R has the same meaning as defined above, and R' denotes an acyl group.

The Fredericamycin A derivatives (I) of this invention may be prepared by either one of the following processes:

position

Since applicants are arguing

A primafacie case of obviousness requires the following: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP at 2143.

In response there is a suggestion in the Kelly reference to include the amino amidino (see the R1 and R2 definition given above.) These are just at a different position.

Applicants have it at the R2 position. or they have an alkyl group with a halogen or the amino group at the R3 position.

Thus the difference is in the positions of the substitutents. This makes them positional isomers. In the pharmaceutical art there is an expectation that positional isomers will retain the properties. That is where one of the motivation to modify the compounds come from. Applicants have not shown any unexpected results with respect to these modifications. The two references combined do teach the limitations and there is a reasonable expectation of success.

With respect to applicants arguments that Duan et al., Delgado et al. and Okimoto et al ,do teach the cyclodextrin inclusive compounds but not the fredicamycim, this may be correct but the US Kelly and the Yokoi reference both talk about making fredricamycin more water soluble to be more effective, which is another motivating factor to modify the compound. Thus from the teachings of Duan et al., Delgado et al. and Okimoto et one would be motivated to use dextrin to make it more water soluble.

See the Background of the invention in US 463, 678.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claim reads R8 can independently defined by R5 and R5 can be H and yet it states it can combine to form a ring!.
- The claim 9 states a "Drugs" without a definition in the spec. Is it a mixture of different drugs if so which or is it a method of treating claims. Then it should be in the "method "or a process format. The claim has been treated and examined as a ""product " claim.
- R24 and R25 each individually is H, CN and also R21 with is another plethora of substitutents, R24 and R25 together is a cycloalkyl .
- R2 is given by

, and the $(CH_2)_r$-chain elongated group $(CH_2)_rCH{=}N\text{-}N\text{-}(C_2NX'R211R212R213R214)$ (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_8 alkyl), -

Where are these 4 R groups attached to? The N? or C3 ? and X' is then attached to? What is meant by a chain elongated group.? Is it (CH2)r ? or something else attached to it? If so what is attached to it?

Conclusion

The examiner called the attorney on 8/5/2010 and left a message, to discuss allowable subject matter. The numerous amendment to the specifications has changed the scope of the examination. The examiner invites the attorney to call and discuss how to make the claims allowable.

Claims 1-7, 9, 15 and 16 stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rita J. Desai/
Primary Examiner, Art Unit 1625

August 6, 2010.